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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MCDONNELL, BOEHNEN, HULBERT AND BERGHOFF, LLP
300 SOUTH WACKER DRIVE
SUITE 3100
CHICAGO, IL 60606

EXAMINER	
EPPS FORD, JANET L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/683,990	Applicant(s) MCSWIGGEN ET AL.	
	Examiner Janet L. Epps-Ford	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 31 October 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3,13-21,30,31,36,38 and 40-50 is/are pending in the application.

4a) Of the above claim(s) 49 and 50 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3,13-21,30,31,36,38 and 40-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Newly submitted claims 49-50 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 1, 3, 13-21, 30, 33, 38, and 40-48 which are drawn to a chemically modified nucleic acid molecule are considered to read on the invention as originally presented, Invention I, classifiable in 536/24.5. However, new claims 49-50 are considered to read on an invention that is directed to a patentably distinct invention, invention II, classifiable in 514/44.

4. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of

using that product. See MPEP § 806.05(h). In the instant case the chemically modified nucleic acid molecule of invention I, can be used in a method of nucleic acid hybridization and/or nucleic acid amplification. Therefore, the product claims of invention I can be used in a materially different method other than the method of invention group II.

5. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 49-50 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. Claims 1, 3, 13-21, 30, 33, 38, and 40-48 are therefore presently pending for examination.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3, 13-21, 30-31, 36, 38 and 40-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

9. The limitation "a chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides...an 18 to 27 nucleotide sequence of the sense strand is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of said human PGF-1 RNA...about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 present of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidines nucleotides present in or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidines nucleotides," recited in the presently amended claim 1, and those claims dependent therefrom, is not supported by the instant specification. There appears to be no written description of this limitation in the specification as filed. See MPEP § 2163.06, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

10. Applicants make reference to several pages of the specification as support for the new limitations in claim 1, ¶ [0029] of the specification as filed described the following:

> [0029] In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides can be used to improve in vitro or in vivo characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

11. This disclosure is directed to a siNA molecule and not to the broad genus of chemically modified nucleic acid molecules recited in the instant claims. Moreover, the instant claims are drawn to wherein the sense strand is independently 18 to 27 in length and ***comprises*** *an* 18 to 27 nucleotide sequence of human PGF-1 RNA. There is no support for this modification to the claims.

12. There is nothing in the specification as filed that would lead on of ordinary skill in the art to the combination of modifications set forth in the claim 1 and those claims dependent therefrom. Thus it appears that the combination of modifications recited in parts (d) and (f) of claim 1 is not found in the specification as originally filed.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 3, 13-21, 30-31, 36, and 38-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since

the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the narrower recitation of "a chemically modified nucleic acid molecule, wherein a) the nucleic acid molecule comprises a sense stand and a separate antisense strand...each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length," and the claim also recites "an 18 to 27 nucleotide sequence of the sense strand is complementary to the antisense strand, *and* *comprises an 18 to 27 nucleotide sequence of the human PGF-1 RNA sequence;*" which is a broader statement of the range/limitation.

16. Claim 1, and those claims dependent therefrom, recite the limitation "*the nucleic acid molecule comprises a sense strand and a separate antisense strand.*" This phrase is vague and indefinite since it is unclear if the scope of the claimed invention is drawn to a single nucleic acid molecule, comprising a sense strand region and further comprises a separate independent region comprising an antisense strand region, *or* if

the claimed nucleic acid molecule is actually in the form of a duplex structure comprising two separate and independent strands corresponding to the recited antisense and sense strands in the claimed invention.

Response to Arguments

Claim Rejections - 35 USC § 103

17. Claims 1, 3, 13-21, 30, 33, and 38, remain rejected and 40-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmeliet et al. (WO 01/85796 A2), in view of GenBank Accession No. NM_002632, Parrish et al. (Molecular Cell 2000, vol. 6, pages 1077-1087), and Agrawal et al. (WO 9401550 A1), for the reasons of record.

18. Applicant's arguments filed 10/31/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the cited references taken together do not provide a reason that would have compelled a skilled artisan to modify a double stranded construct such as the one recited in the instant claims. Moreover, Applicants argue that the cited references do not teach the skilled person how to narrow down or predict which of the exceedingly large number of potential modified constructs may retain RNAi activities.

19. Contrary to Applicant's assertions, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the potential modified constructs retain RNAi activity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

20. Furthermore, contrary to Applicant's assertion that the cited references taken together do not provide a reason that would have compelled a skilled artisan to modify a double stranded construct such as the one recited in the instant claims, the cited art clearly compel the skilled artisan to design nucleic acid inhibitors targeting human placental growth factor-1, and further provide compelling reasons for introducing chemical modifications into the nucleic acid inhibitor.

As stated in the prior Office Action, Carmeliet et al. provide compelling reasons to design nucleic acid modulators of placental growth factor, namely as research tools for the study of pathological angiogenesis, see page 8, lines 1-14 of this reference. The sequence of human placental growth factor 1 as set forth in the instant claims as SEQ ID NO: 257 was previously disclosed in GenBank Accession No. NM_002632. Moreover, the prior art taught that chemically modified oligonucleotides, of DNA or RNA, comprising a partially or completely double-stranded portion, have improved properties over typical antisense oligonucleotides, particularly in regards to nuclease degradation resistance, while maintaining the ability to modulate the expression of a target gene, see Agrawal et al. In regards to the modification of siRNA Elbashir et al. taught teach that siRNAs containing nucleotide modifications known in the art such as 2'-OMe substitutions can stimulate RNA interference. Moreover, Parrish et al. taught that some common nucleotide modifications, including sugar modifications such as 2'-fluoro, base modifications such as 5-modified uridines and phosphorothioate backbones are tolerated in interfering RNAs.

Applicant's response, it is argued that Parrish does not inform the selection of a double stranded nucleic acid molecule of the claimed length, let alone the specific types, patterns and levels of modifications claimed. Moreover, Applicants argue that Parrish can be said to teach away from 2'-deoxy modifications of cytidine, and therefore teach away from 2'-deoxy-2'-fluoro pyrimidine modifications as recited in the instant claims. Moreover, Applicant's argued that Elbashir et al. teaches away from modifying siRNA molecules at any other position besides the terminal ends.

Contrary to Applicant's assertions, Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5). Moreover, both Elbashir et al. and Parrish et al. are not considered to teach away, but rather to support that it was known in the art to test various chemical modifications in double stranded nucleic acid molecules to optimize the activity therein.

Elbashir et al. and Parrish et al. each teach incorporating chemical modifications into dsRNA molecules, chemical modifications that were known in the art to benefit the delivery of other nucleic acid therapeutics such as antisense oligonucleotides and/or ribozymes. It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicants argue that neither Elbashir nor Parrish teach or suggest the presence of 2'-O-methyl purine and 2'-deoxy-2'-fluoro pyrimidine nucleotides in a single double stranded nucleic acid molecule and assert that the combined teachings do not suggest all limitations of the claims. While it is correct that the cited references do not explicitly teach modification of purines with 2'-Omethyl and pyrimidines with 2'-fluoro, the person of ordinary skill would recognize that production of nucleic acids of any sequence and pattern of modification is a matter of design choice made in the course of routine optimization.

In regards, to Agrawal et al. Applicants argue that since the disclosure of this reference is drawn to self-stabilized oligonucleotides, that its disclosure fails to teach a nucleic acid molecule comprising a sense strand and a separate antisense strand, as claimed. Contrary to Applicant's assertions, to the extent that the phrase "a separate antisense strand" is recited with respect to the claimed *"a"* chemically modified nucleic acid (*it is noted that the term "double-stranded" was* removed from the preamble), which comprises both the sense and antisense strand, it remains that the self-stabilized oligonucleotides of Agrawal et al. read on the claimed invention. Applicants have not clearly defined what they mean in regards to the limitation "a separate antisense strand," see the above rejection under 35 USC § 112, 2nd.

It is noted that Applicant's did not address the merits of the instant rejection with regards to the teachings of Carmeliet et al. with respect to the combination of its teachings with the other cited references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, Applicants have not provided any evidence of unexpected results with respect to the full scope of the plurality of chemically modified nucleic acids encompassed by the instant claims that would clearly suggest non-obviousness over the cited references. Applicant's arguments are not sufficient to provide evidence of non-obviousness of the claimed invention.

Therefore, as stated in the prior Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the cited references to make double stranded nucleic acid molecules capable of down-regulating the placental growth factor-1 gene (PGF-1). Carmeliet et al. teach the use of nucleic acid based inhibitors, including antisense DNA and RNA as a means to antagonize the activity of PGF-1. Elbashir et al. provide a motivation to make and design double stranded nucleic acid inhibitors to inhibit the expression of a target gene. Parrish et al. provide a motivation to use double stranded nucleic acid containing modified sugar, base and backbone modifications, teaching that such modifications, which are well-known and routinely used in the antisense field, are tolerated in RNA interference. One of ordinary skill in the art would have had a reasonable expectation of success in making double stranded nucleic acid to down-regulate the expression of the PGF-1 gene because Carmeliet et al. teach that PGF-1 gene expression can be inhibited by the activity of RNA inhibitors, and Elbashir et al. and Parrish et al. teach the feasibility of designing a dsRNA molecule to inhibit the activity of a target gene having a known nucleotide sequence (see GenBank Accession No. NM_002632).

One of ordinary skill in the art would have had a reasonable expectation of success in making double stranded nucleic acid having sugar, base and backbone modifications because Elbashir et al. and Parrish et al. each teach that interfering RNAs containing such modifications are active in provoking RNA interference. Furthermore, Agrawal et al. clearly teach that stabilized nucleic acid, DNA or RNA, comprising modifications and a double stranded structure was effective in inhibiting the expression of a target gene.

Moreover, it would have been obvious to modify the teachings of the cited references to design siRNA molecules targeting human placental growth factor 1 of SEQ ID NO: 257, and further comprising the various modifications described by Parrish et al., Elbashir et al., and Agrawal et al. since these references provide teachings to guide the ordinary skilled artisan to modify the siRNA molecule to comprise 2'-O-methyl modifications, 2'-fluoro modifications, for the purpose of increasing nuclease resistance, without the loss of RNAi activity.

Double Patenting

21. Claims 1 3, 13-21, 30, 33, and 37-39 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/922,761. Applicants stated that they would file a terminal disclaimer at the appropriate time. However, Applicants did not provide any arguments to address the merits of the rejection therefore; the instant claims remain rejected for the reasons of record.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE